25
Enantioselective Hydrogenation of Alkenes with Ferrocene-Based Ligands

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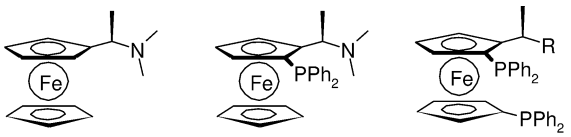
25.1
Introduction

Ferrocene as a (at the time rather exotic) backbone for chiral ligands was introduced by Kumada and Hayashi [1] based on Ugi's pioneering studies related to the synthesis of enantiopure ferrocenes (Fig. 25.1). Ppfa, as well as bppfa and bppfoh, proved to be effective ligands for a variety of asymmetric transformations. From this starting point, several ligand families with a range of structural variations have been developed during the past few years. In this chapter we will describe effective ligand structures developed over time, the main focus being on diphosphine derivatives (Fig. 25.2) and their application to the hydrogenation of alkenes. Three recently published reviews cover some of the same area, but from slightly different points of view. Colacot and Barbaro et al. [2] presented general overviews on ferrocene-based chiral ligands and their application to various asymmetric transformations, while Blaser et al. [3] and Tang and Zhang [4] reviewed the recent progress in the application of diphosphines for the enantioselective hydrogenation. These reviews can serve to put the present account into a broader perspective.

This chapter is organized according to the position of the phosphine groups **P**, as depicted in Fig. 25.2. It is important to realize that many of the ligands described here have both planar (C_p ring with two different substituents) as well



Ugi amine (*R,S*)-ppfa bppfa R = NMe_2 bppfoh R = OH

Fig. 25.1 Structures of Ugi's amine and the first ferrocene-based chiral phosphine ligands.

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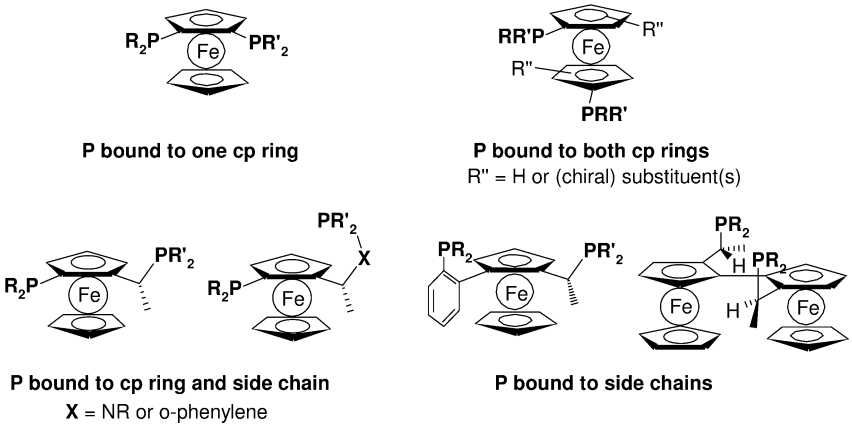


Fig. 25.2 Subclasses of ferrocenyl diphosphines.

as central (in the side chain) chirality. In most cases, the central chirality dominates the sense of induction, but strong matched-mismatched effects are very common. Except for selected cases we will not include the absolute configuration in the ligand names, but as a rule the central chirality is given first, followed by the planar and (if applicable) the axial chirality (e.g., see ppfa in Fig. 25.1).

When assessing catalytic results reported for new ligands, one must bear in mind that their quality and relevance differ widely. For most new ligands only experiments with selected model test substrates carried out under standard conditions are available, and very few have already been applied to industrially relevant problems. The test substrates for alkenes used most frequently are Acetamido Cinnamic Acid (ACA) or its methyl ester (MAC), Methyl Acetamido Acrylate (MAA), ITaconic Acid or DiMethyl ITaconate (ITA, DMIT) and selected aryl enamides (Fig. 25.3).

Especially for new ligands, reaction conditions are usually optimized for enantioselectivity, whereas catalyst productivity (given as turnover number, TON, or substrate/catalyst ratio, SCR) and catalyst activity (given as turnover frequency, TOF (h^{-1}), at high conversion) are often only a first indication of the potential of the ligand. The decisive test – namely the application of a new ligand to "real world problems" which will tell about the scope and limitations of a ligand (family) concerning tolerance to changes in the substrate structure and/or the presence of functional groups – will often come much later.

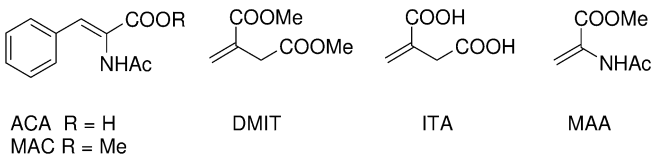


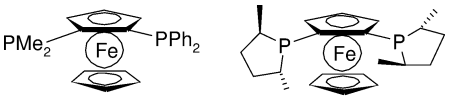
Fig. 25.3 Structures and abbreviations of frequently used model test substrates.

25.2
Ligands with Phosphine Substituents Bound to One Cyclopentadiene Ring

Until now, only a few effective ligands of this type have been identified (Fig. 25.4). Kagan and co-workers [5] prepared one of the few chiral diphosphines with only planar chirality and obtained 95% ee for the hydrogenation of DMIT with **L1** (Table 25.1, entry 1.1.), but enantioselectivities for several enamide derivatives were below 82% ee (the best results were with the cyclohexyl analogue of **L1**). For the reactions with DMIT or MAC, the cationic Rh-kephos complex showed comparable or better performance than corresponding duphos catalysts.

25.3
Ligands with Phosphine Substituents Bound to both Cyclopentadiene Rings

As noted earlier, the first effective ligands were prepared by Kumada and Hayashi during the 1970s, starting from Ugi's amine. Depending on the reaction conditions, phosphine substituents were introduced either on one or on both cyclopentadiene rings. It transpired that only the diphosphines bppfa and bppfoh were useful for hydrogenation reactions. Only recently, new, usually C_2 symmetrical, ligand families were prepared with excellent catalytic properties for a variety of hydrogenation reactions (Fig. 25.5).



L1 kephos

Fig. 25.4 Structures and abbreviations of diphosphines with P bound to one C_p ring.

Table 25.1 Selected results for Rh-catalyzed hydrogenations using diphosphines having both P bound to one C_p ring (for structures, see Fig. 25.4).

Entry	Ligand	Substrate	p(H_2) [bar]	SCR	TOF [h^{-1}]	ee [%]	Comments	Reference
1.1	**L1**	DMIT	1	100	n.a.	95		5
1.2	kephos	DMIT	10	1000	1000	99.5	ee > 99.9% at SCR 200	6
1.3	kephos	MAC	10	1000	300	96	ee 98% at SCR 200	6

SCR = substrate:catalyst ratio; n.a. = not available.

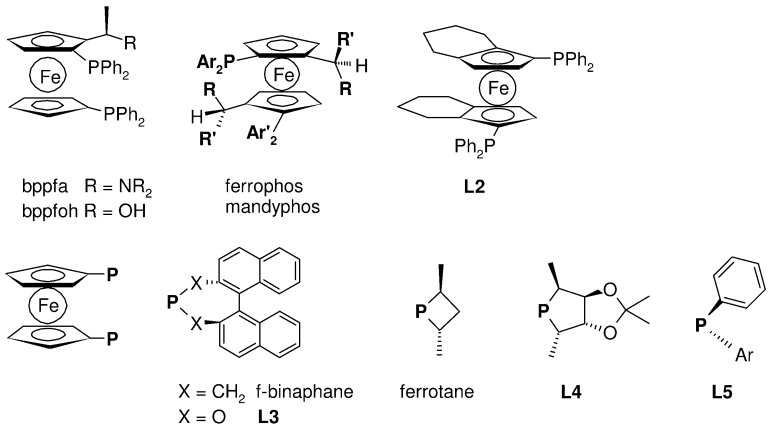


Fig. 25.5 Generic structures and names or numbers of ferrocene-based diphosphines with P bound to both C_p rings.

25.3.1
Bppfa, Ferrophos, and Mandyphos Ligands

Bppfoh and bppfa derivatives have been applied most successfully for the Rh-catalyzed hydrogenation of dehydro amino acid derivatives such as MAC (ee 97%) and of functionalized ketones [7]. The nature of the amino group has a significant effect on enantioselectivity and often also on activity, and is used to tailor the ligand for a particular substrate. Rh-bppfa complexes were among the first catalysts able to hydrogenate tetrasubstituted C=C bonds, albeit with relatively low activity (Table 25.2, entries 2.1–2.3). Ferrophos, one of the very few li-

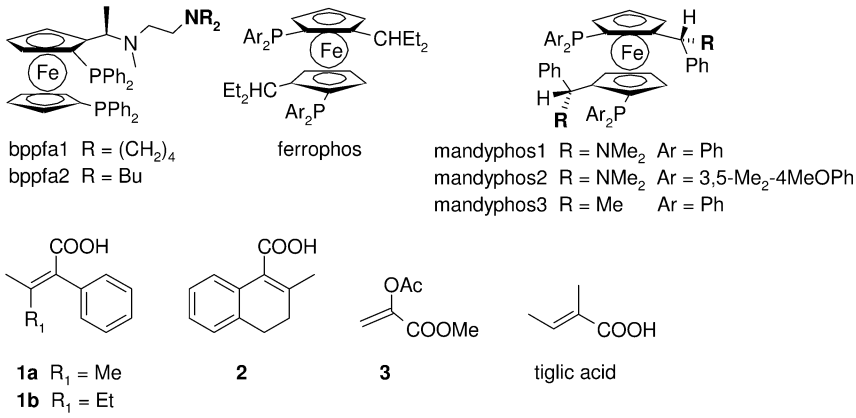


Fig. 25.6 Structures of specific bppfa, ferrophos, and mandyphos ligands and of test substrates.

Table 25.2 Selected results for Rh-catalyzed hydrogenations using bppf, ferrophos, and mandyphos derivatives (for structures, see Figs. 25.5 and 25.6)

Entry	Ligand	Substrate	$p(H_2)$ [bar]	SCR	TOF [h^{-1}]	ee [%]	Comments	Reference
2.1	bppfa1	**1a**	50	200[a)]	7[a)]	98.4		7
2.2	bppfa1	**1b**	50	200[a)]	2[a)]	97	*cis*/*trans* 97/3	7
2.3	bppfa2	**2**	50	100[a)]	2[a)]	87	*cis*/*trans* >99/1	7
2.4	ferrophos	ACA	2	100[a)]	~10–30	98.9	97.6% ee for MAC	8
2.5	Mandyphos1	pCl-MAC	1	100[a)]	n.a.	>99	98% ee for MAC	9c
2.6	Mandyphos2	MAC	1	20000	~3000	98.7	>99% ee at SCR 200	9d
2.7	Mandyphos2	tiglic acid	5	200[a)]	11[a)]	97	Ru complex	9d
2.8	Mandyphos3	MAC	1	100[a)]	≥600[a)]	98.6	97.9% ee for MAA	9b
2.9	Mandyphos3	**3**	1	100[a)]	8[a)]	95		9a

a) Standard test results, not optimized.

gands with only planar chirality, shows good ee-values but low activity for dehydroamino acid derivatives (Table 25.2, entry 2.4).

Mandyphos ligands [9] are highly modular bidentate analogues of ppfa where not only the phosphine moieties but also the R substituent have been used for fine-tuning purposes. Both C_2 (Ar = Ar′) as well as C_1 (Ar ≠ Ar′) symmetrical ligands have been prepared and tested in an extended screening [9d]. Even though the scope of this family is not yet fully explored, these test results indicate high enantioselectivities as well as high activity for the Rh-catalyzed hydrogenation of dehydroamino acid derivatives (Table 25.2, entries 2.5, 2.6, 2.8), tiglic acid (Ru complex, entry 2.7) and enol acetate **3** (entry 2.9). Mandyphos2 was shown to be the most versatile ligand, leading to very high TON and TOF for the MAC hydrogenation (entry 2.6). Both enantiomers of the mandyphos family are equally well accessible, and selected derivatives are now commercialized by Solvias in collaboration with Umicore (formerly OMG) [10].

25.3.2 Miscellaneous Diphosphines

A variety of C_2 symmetrical diphosphine ligands with a ferrocenyl backbone (see Fig. 25.5) have recently been described and tested, with sometimes quite impressive results. Interesting examples are f-binaphane [11], ferrotane [12], **L2**

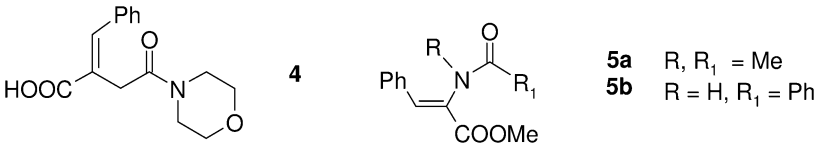


Fig. 25.7 Structures of substrates listed in Table 25.3.

Table 25.3 Selected results for Rh-catalyzed hydrogenations using miscellaneous diphosphines (for structures of ligands, see Fig. 25.5; for structures of substrates, see Fig. 25.7).

Entry	Ligand	Substrate	$p(H_2)$ [bar]	SCR	TOF [h^{-1}]	ee [%]	Comments	Reference
3.1	Ferrotane [a]	4	5	20 000	~7000	98–99	98% ee for DMIT	12
3.2	**L2**	MAC	1	1 000 [b]	40 [b]	97	96% for MAA	13
3.3	**L3**	DMIT	1.3	5 400	270	>99.5		14
3.4	**L4**	ITA	5	100 [b]	<10 [b]	99.5	ee 90% for DMIT	15
3.5	**L4**	MAA	3	10 000	850	99.9	best solvent THF	15
3.6	**L4**	MAC [c]	1	100 [b]	100 [b]	>99.9	best solvent THF	15
3.7	**L5**	5a	1	200 [b]	15 [b]	97	Ar 2-anisyl	16b
3.8	**L5**	5b	2	100 [b]	15 [b]	98.5	Ar 9-phenanthryl	16c

a) Et-ferrotane.
b) Standard test results, not optimized.
c) Various substituted analogues were tested.

with only planar chirality [13], bisphosphonite **L3** [14], the sugar-based phospholane **L4** [15] and the P-chiral phosphines **L5** [16].

Rh complexes of ferrotanes showed very good performance for various amido itaconates, and achieved very high TONs and TOFs for substrate **4** (Table 25.3, entry 3.1). The planar chiral Rh-**L2** complex achieved up to 97% ee for MAC (entry 3.2) and bisphosphonite **L3** based on a binol or related moiety achieved very high ee-values and respectable TONs for the hydrogenation of itaconates (entry 3.3). The sugar-based ligand **L4** is excellent for dehydroamino and itaconic acid derivatives, with good TONs and very high ee-values (entries 3.4–3.6). Rh-**L5** complexes (with Ar = 2-anisyl, 1-naphthyl or 9-phenanthryl) reduce MAC and ACA with ee-values of 95–99% (results not shown). In contrast to many other ligands, Rh-**L5** catalysts are quite tolerant towards changes in the structure of the amide moiety, showing high ee-values for N-methyl (**5a**, entry 3.7) or benzoyl derivatives (**5b**, entry 3.8).

25.4
Ligands with Phosphine Substituents Bound to a Cyclopentadiene Ring and to a Side Chain

The first successful variation of the ppfa structure was carried out by Togni and Spindler, who replaced the amino group at the stereogenic center of the side chain by a second phosphino moiety. Later, very effective ligands were also obtained when a further bridging group was introduced between the stereogenic center and the second phosphino group, as in bophoz or **L7** (Fig. 25.8).

25.4.1
Josiphos

The josiphos ligands arguably constitute the most versatile and successful ferrocenyl ligand family. Because the two phosphine groups are introduced in consecutive steps with very high yields (as shown in Scheme 25.1), a variety of ligands is readily available with widely differing steric and electronic properties. A comprehensive review on the catalytic performance of josiphos ligands has recently been published [17]. Until now, only the (*R, S*)-family (and its enantiomers) but not the (*R, R*) diastereomers have led to high enantioselectivities (the first descriptor stands for the stereogenic center, the second for the planar chirality). The ligands are technically developed, and available in commercial quanti-

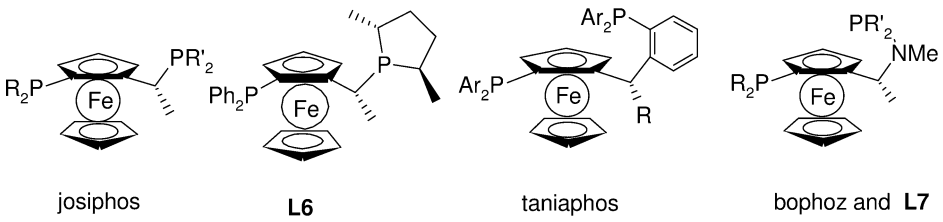
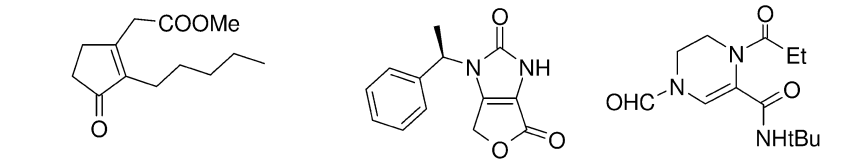


Fig. 25.8 Structures and names of the most important diphosphines with P bound to a C_p ring and a chiral side chain.



Ru - josiphos or duphos; ee 90%
TON 2,000; TOF 200 h^{-1}
medium scale production
Firmenich

Rh - josiphos; de 99%
TON 2,000; TOF n.a.
medium scale production
Lonza

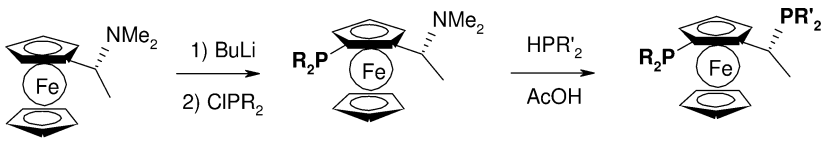
Rh - josiphos; ee 97%
TON 1,000; TOF 450 h^{-1}
pilot process, >200 kg
Lonza

Fig. 25.9 Industrial applications of josiphos ligands for (for further information, see [19]).

6 **7**

8a R_1 = Me, R_2 = $(CH_2)_4OR$, R_3 = Me
8b R_1 = Me, R_2 = Hex, R_3 = Me
8c R_1 = $Cy(CH_2)_2$, R_2 = $(CH_2)_4Cl$, R_3 = Me

Fig. 25.10 Structures of substrates listed in Table 25.4.



R and R': substituted aryl, alkyl, cycloalkyl

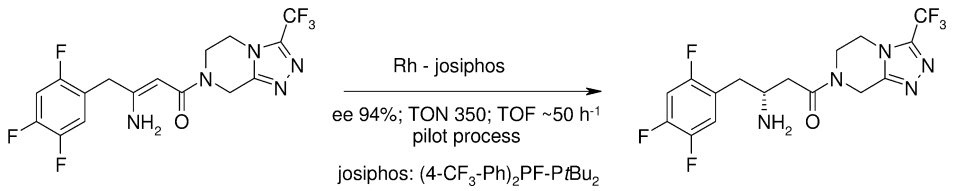
Scheme 25.1 Preparation of josiphos ligands starting from the Ugi amine.

ties from Solvias [10]. The most important application is undoubtedly the hydrogenation of C=N functions where the largest enantioselective process has been realized for the enantioselective production of the herbicide (*S*)-metolachlor [18] and of highly substituted C=C bonds. Several smaller productions and some pilot processes use josiphos ligands and important examples are shown in Fig. 25.9.

Table 25.4 Selected results for the Rh- and Cu-catalyzed hydrogenation using josiphos ligands (for structures, see Figs. 25.8 and 25.10).

Entry	Substrate	Metal-ligand (R, R′) [a]	p(H_2) [bar]	SCR	TOF [h^{-1}]	ee [%]	Reference
4.1	ACA	Rh-(3,5-$(CF_3)_2$Ph, Cy)	1	600	>600	99	6
4.2	MAA	Rh-(3,5-$(CF_3)_2$Ph, Cy)	1	600	>600	98	6
4.3	MAA	Rh-(Ph, Cy)	1	100 [b]	330 [b]	97	17
4.4	DMIT	Rh-(Ph, Cy)	1	100 [b]	200 [b]	99.9	17
4.5	DMIT	Rh-**L6**	1	200 [b]	200 [b]	99.5	20
4.6	**6**	Rh-(3,5-$(CF_3)_2$Ph, Cy)	1	100 [b]	90 [b]	92	4
4.7	**7**	Cu-(Ph, Cy)	[c]	100 [b]	~16 [b]	94	21
4.8	**8a**	Cu-(Ph, Cy)	[c]	1640	~75	98	22
4.9	**8b**	Cu-(Ph, Cy)	[c]	100 [b]	>10 [b]	99	22
4.10	**8c**	Cu-(Ph, Cy)	[c]	100 [b]	>10 [b]	99	22

a) See Fig. 25.8, Cy = cyclohexyl.
b) Standard test results, not optimized.
c) Reducing agent: polymethylhydrosiloxane/NaO*t*Bu.



Scheme 25.2 Hydrogenation of the *β*-dehydro amino acid amide intermediate for MK-0431.

As can be seen from Table 25.4, several Rh-josiphos complexes are excellent catalysts for the hydrogenation of *α*-dehydro amino acid derivatives and DMIT with ee-values of 97–99.9% (entries 4.1–4.5). While the reactions have not been optimized, satisfactory TONs and TOFs have been observed. Good ee-values are also obtained for a *β*-dehydro amino acid derivative (entry 4.6) and for the Cu-catalyzed reduction with PMHS of activated C=C bonds (entries 4.7–4.10), albeit with relatively low TOFs. Interestingly, in all cases the best ligands have unsubstituted or electron-deficient aryl groups on the ring phosphorus and a PCy_2 group at the side chain.

Recently, Merck chemists reported the Rh-josiphos-catalyzed hydrogenation of unprotected dehydro *β*-amino acids with ee-values up to 97%, but relatively low activity [23]. It was also shown that not only simple derivatives but also the complex intermediate for MK-0431 depicted in Scheme 25.2 can be hydrogenated successfully, and this has been produced on a >50 kg scale with ee-values up to 98%, albeit with low to medium TONs and TOFs [24].

25.4.2
Immobilized Josiphos and Josiphos Analogues

Several josiphos ligands were functionalized at the lower C_p ring and grafted to silica gel or a water-soluble group [25a] to give very active catalysts for the Ir-catalyzed MEA imine reduction; a Rh-josiphos complex grafted to several dendrimers (e.g., see Fig. 25.11) hydrogenated DMIT with ee-values up to 98.6% with similar activities as the mononuclear catalyst [25b]. Salzer and co-workers [20] prepared a number of josiphos analogues based on an arene chromium tricarbonyl scaffold (**L8**) and tested their Rh complexes on several alkenic substrates. With few exceptions, relatively low ee-values and catalyst activities were observed: ≤79% ee for DMIT, ≤87% for MAC, ≤91% for MAA, and ≤85% for the *β*-dehydro amino acid derivative **6**. Weissensteiner and co-workers [26] described two josiphos analogues **L9** and **L10** with restricted rotation of the side chain, and observed a strong decrease in enantioselectivity (best ee ≤91% for DMIT with **L10**, R′ = Cy).

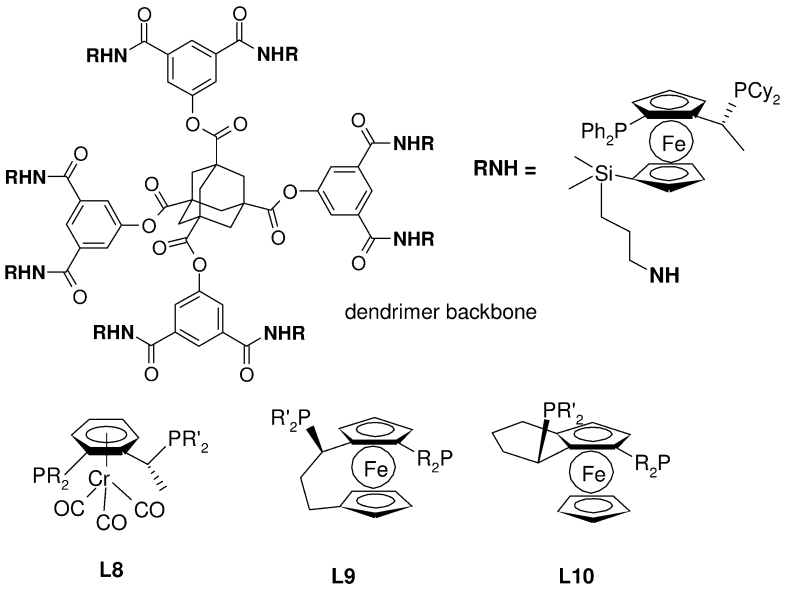
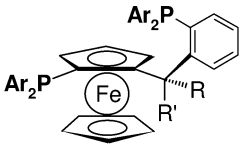


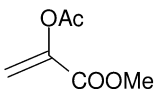
Fig. 25.11 Structure of immobilized josiphos and josiphos analogues.

25.4.3 Taniaphos

Compared to the josiphos ligands, taniaphos ligands have an additional phenyl ring inserted at the side chain of the Ugi amine. Whereas the effect of changing the two phosphine moieties has only been investigated with a few derivatives (Table 25.5, entries 5.3, 5.4, 5.5, 5.8–5.10), the nature of the substituent at the stereogenic center has a strong effect on the induction of stereochemistry for the Rh-catalyzed hydrogenation of MAC and DMIT. Rather surprisingly, a change of the substituent can even lead to a different sense of induction. For MAC, methyl or methoxy substituents lead to the opposite absolute configuration of the product compared to R = NMe_2, *i*-Pr or H (entries 5.1–5.4). Similar effects are also observed for DMIT (entries 5.7– 5.11) and for the hydrogenation of enol acetate **9** where ee-values up to 98% but low activities are achieved (entry 5.13). Interestingly, changing the absolute configuration of the stereogenic center only has an effect on the level of the ee but not on the sense of induction (compare entries 3/4 and 7/8). Enamides **10** are hydrogenated with high ee-values but low TOFs (entries 5.14 and 5.15). Currently, several taniaphos ligands are being marketed by Solvias in collaboration with Umicore (formerly OMG) [10].



taniaphos



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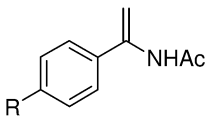


a R = H
b R = Br
c R = Me

10

Fig. 25.12 Structure of taniaphos derivatives and substrates listed in Table 25.5.

Table 25.5 Selected results for Rh-catalyzed hydrogenations using taniaphos (Ar = Ph, pH_2 1 bar) (for structures, see Fig. 25.12).

Entry	Ligand (R, R′)	Substrate	p(H_2) [bar]	TON [a]	TOF [a] [h^{-1}]	ee [%]	Comments	Reference(s)
5.1	(H, *i*Pr)	MAC	1	100	25	97 (*R*)	52% (*S*) for R′ = Me!	27a
5.2	(H, NMe_2)	MAC	1	100	200	95 (*R*)	77% (*R*) for R′ = H	27a
5.3	(H, OMe)	MAC	1	100	50	94 (*S*)	92% (*S*) for Ar = Xyl	27b
5.4	(OMe, H)	MAC	1	100	67	99 (*S*)	99% (*S*) for Ar = Xyl	27b
5.5	(H, NMe_2)	MAC	1	200	>200	99.5 (*S*)	Ar = 3,5-Me_2-4-MeOPh	6, 27c
5.6	(H, NMe_2)	MAA	1	200	106	97	Ar = 3,5-Me_2-4-MeOPh	6, 27c
5.7	(H, *i*Pr)	DMIT	1	100	25	98 (*S*)	19% (*R*) for R′ = Me!	27a
5.8	(H, NMe_2)	DMIT	1	100	7	91 (*S*)	75% (*S*) for R′ = H [b]	27a
5.9	(H, NMe_2)	DMIT	1	200	>200	99.5 (*S*)	Ar = 3,5-Me_2-4-MeOPh	6, 27c
5.10	(OMe, H)	DMIT	1	100	200	98 (*R*)	90% (*R*) for Ar = Xyl	27b
5.11	(H, OMe)	DMIT	1	100	40	95 (*R*)		27b
5.12	(H, NMe_2)	**6**	1	100	27	99.5 (*S*)	Ar = 3,5-Me_2-4-OMePh	6, 27c
5.13	(OMe, H)	**9**	1	100	5	98 (*S*)	80% (*S*) for (O, OMe)	27b
5.14	(OMe, H)	**10a**	1	100	7	96	97% ee for **10b**	27b
5.15	(OMe, H) [c]	**10a**	1	100	67	92	95% ee for **10c**	27b

a) Standard test results, not optimized.
b) At 10 bar, low conversion at 1 bar.
c) Ar = Xyl.

25.4.3 Various Ligands

Bophoz [28] and **L11** [29] are modular ligands with a PR_2 group on the C_p ring and an aminophosphine or a phosphoramidite, respectively, at the side chain. Bophoz ligands are air-stable and effective for the Rh-catalyzed hydrogenation of a variety of enamides and itaconates with high ee-values, TONs and TOFs (Table 25.6, entries 6.1–6.3); depending on the solvent the stability of the N–PR_2 bond might be a critical issue. As observed for several ligands forming seven-membered chelates, high activities can be reached (maximum TOFs up 68 000 h^{-1}) and TONs up to 10 000 have been achieved [28c]. A feasibility study for the

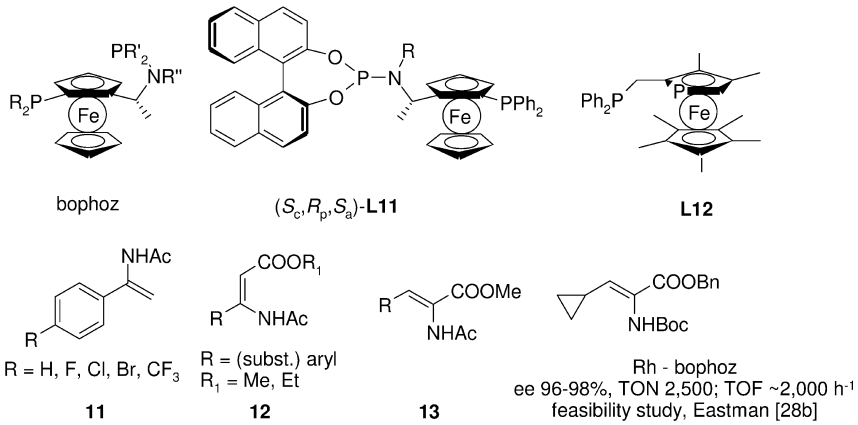


Fig. 25.13 Structures of bophoz, **L11**, **L12** and of substrates listed in Table 25.6.

preparation of enantiopure cyclopropylalanine has been reported (Fig. 25.13). Ligands of the type **L11** have three elements of chirality (central, planar, and axial), and all combinations were actually prepared and tested for enamides **11**. As can be seen comparing entries 6.4–6.7 in Table 25.6, the absolute configuration of the binaphthol moiety determines the absolute configuration of the product; the relative configurations of the other chiral elements have a variable but usually very strong effect on the magnitude of the ee. Best results were achieved for the (S_c,R_p,S_a)-**L11** diastereomer shown in Fig. 25.13 (entry 6.8), which also shows very high enantioselectivities and very good TONs and TOFs for DMIT (entry 6.9). MAC was also hydrogenated very effectively, but only when 2 equiv. of ligand were added (entry 6.10); *β*-dehydroamino esters **12** are also good substrates for Rh/**L11** catalysts (entries 6.11, 6.12). Ligand **L12** with only planar chirality does not quite fit in this category since one of the P atoms is not attached to but is part of the C_p ring. The corresponding Rh complexes achieve respectable ee-values for several dehydroamino esters, but have very low activity (entry 6.13).

25.5
Ligands with Phosphine Substituents Bound only to Side Chains

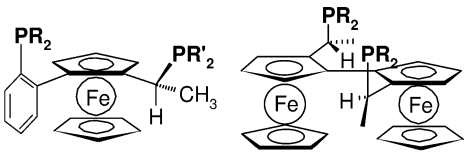
Until now, only two families of ligands have been realized where both P groups are attached to side chains, probably because the resulting metal complexes have relatively large chelate rings which usually are not suitable for enantioselective catalysis. A cursory inspection of the ligands depicted in Fig. 25.14 shows that, due to steric bulk of the ferrocene backbone, both diphosphines probably have sufficiently restricted flexibility so that good stereocontrol is still possible.

The starting point for walphos was also the Ugi amine. Like josiphos, walphos ligands are modular but form eight-membered metallocycles due to the

Table 25.6 Selected results for Rh-catalyzed hydrogenation using bophoz, **L11**, and **L12** (for structures, see Fig. 25.13).

Entry	Ligand	Substrate	p(H_2) [bar]	SCR	TOF [h^{-1}]	ee [%]	Comments	Reference
6.1	bophoz[a]	MAC	~1	10000	10000	97	99.4% ee for MAA	28c
6.2	bophoz[a]	subst MAC	~1	100[b)]	~100[b)]	97–99	various derivatives	28c
6.3	bophoz[c]	subst ITA	~3	2500	n.a.	94–99	various derivatives	28c
6.4	(S_c,R_p,S_b)-**L11**	**11** (R=H)	10	100[b]	100[b)]	99.6	(*R*)-product	29a
6.5	(S_c,R_p,R_b)-**L11**	**11** (R=H)	10	100[b)]	100[b)]	11	(*S*)-product	29a
6.6	(S_c,S_p,R_b)-**L11**	**11** (R=H)	10	100[b)]	100[b)]	99.6	(*S*)-product	29a
6.7	(S_c,S_p,S_b)-**L11**	**11** (R=H)	10	100[b)]	100[b)]	83	(*R*)-product	29a
6.8	(S_c,R_p,S_b)-**L11**	**11** (R=H)	10	5000	5000	99.3	for other R ee ~99%	29a
6.9	(S_c,R_p,S_b)-**L11**	DMIT	10	10000	20000	>99		29a
6.10	(S_c,R_p,S_b)-**L11**	MAC	10	10000	10000	>99	2 equiv. ligand	29a
6.11	(S_c,R_p,S_b)-**L11**	**12**	10	100[b)]	~80[b)]	97–>99	ee >99% for R=H	29b
6.12	(S_c,R_p,S_b)-**L11**	**12** (R=H)	10	5000	~4000	97	ee 98% at S/C 1000	29b
6.13	**L12**	**13** (R=Et)	1	20[b)]	<2[b)]	96	MAC 87% ee	30

a) R, R'=Ph, R''=H or Me at SCR 100, ee 99.1%.
b) Standard test results, not optimized.
c) R, R'=Ph, R''=H or Me.



walphos trap

Fig. 25.14 Structures and names of walphos and trap ligands.

Table 25.7 Selected results for Rh- and Cu-catalyzed hydrogenation using (R,R′)-walphos and R-trap ligands (for ligand and substrates structures, see Figs. 25.14 and 25.16, respectively).

Entry	M – (R, R′)	Substrate	$p(H_2)$ [bar]	SCR[a]	TOF $[h^{-1}]$[a]	ee [%]	Comments	Reference(s)
7.1	Rh-(Ph, Ar_1)[b]	MAC	1	200[b]	≥10 b[b]	95	ee 94% for Ar′ = Ph	31 b
7.2	Rh-(Ph, Ar_1)[b]	DMIT	1	200[b]	≥10 b[b]	92		31 b
7.3	Cu-(Ph, Ar_2)[c]	**8**	[c]	100	>10	97	R_1 Me, R_2 $(CH_4)_2OR$, R_3 Et	22
7.4	Cu-(Ph, Ar_2)[c]	**8**	[c]	100	>10	97	R_1 *t*Bu, R_2 Bu, R_3 Me	22
7.5	Rh-Ph-trap[d]	**14a**	50	100	50[c]	94 (*R*)	ee 7% (*S*) without Cs_2CO_3	33 a
7.6	Rh-Ph-trap[d]	**14b**	50	100	200	95	ee 78% for Boc derivative	33 a
7.7	Rh-Et-trap[f]	MAA	0.5	100	50[e]	96 (*R*)	ee 70/2%(!) at 1/100 bar	33 b
7.8	Rh-*i*Bu-trap	MAC	1	100	4	92 (*S*)	R = Et[f] ee 77% (*R*)!	33 b
7.9	Rh-Et-trap[g]	ITA	1	200	30	96	ee 68% for DMIT	33 c
7.10	Rh-Pr-trap	**15**, **16a**	1	100	4	97	ee 82% for **16b**	33 e, f
7.11	Rh-*i*Bu-trap	**17**	1	100	5	97	intermediate for indinavir	33 d

a) Standard test results, not optimized.
b) Ar_1 = 3,5-Me_2-4-MeO-Ph.
c) Ar_2 = 3,5-$(CF_3)_2$-Ph, reducing agent PMHS/NaO*t*Bu.
d) In presence of Cs_2CO_3.
e) At 60 °C.
f) For R = Pr/Ph/*i*Pr, ee = 85% (*R*)/21% (*S*)/5% (*S*), respectively.
g) For R = *i*Bu, ee = 17%.

additional phenyl ring attached to the cyclopentadiene ring [31]. They also show promise for the enantioselective hydrogenation of dehydroamino and itaconic acid derivatives (Table 25.7, entries 7.1 and 7.2), and the Cu-catalyzed enantioselective reduction of *α,β*-unsaturated ketones **8** (entries 7.3 and 7.4). There are noticeable electronic effects, but the scope of this ligand family is still under investigation; several derivatives are available from Solvias on a technical scale [10]. The first industrial application has just been realized in collaboration with Speedel/Novartis for the hydrogenation of SPP100-SyA, a sterically demanding *α,β*-unsaturated acid intermediate of the renin inhibitor SPP100 (Fig. 25.15). The process has already been operated on a multi-100 kg scale.

The trap (*trans*-chelating phosphines) ligands developed by Ito and co-workers [33] form nine-membered metallocycles where trans-chelation is possible. However, it is not clear whether the *cis* isomer which has been shown to be present in small amounts or the major *trans* isomer is responsible for the catalytic activ-

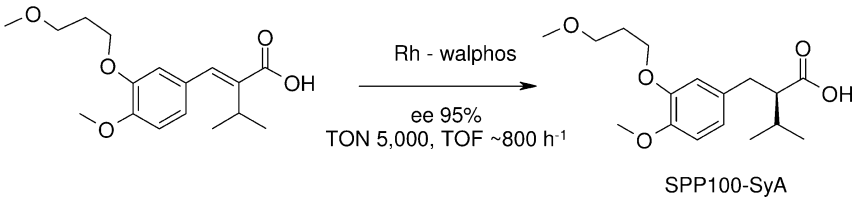


Fig. 25.15 Pilot-scale application of the walphos ligand (R = Ph, R′=3,5-$(CF_3)_2$-Ph) [32].

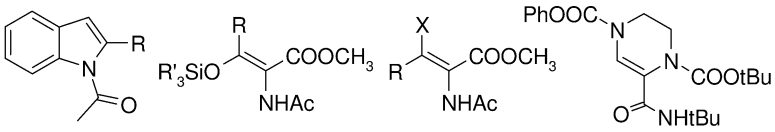


Fig. 25.16 Substrate structures listed in Table 25.7.

ity. Until now, only a few different PR_2 fragments have been tested, but it is clear that the choice of R strongly affects the level of enantioselectivity and sometimes even the sense of induction (e.g., see Table 25.7, entries 7.7 and 7.8). The Rh complexes function best at very low pressures of 0.5–1 bar, but often need elevated temperatures (e.g., entry 7.7). Effectively reduced are indole-derivatives **14** (entries 7.5, 7.6, the first examples of heteroaromatic substrates with high ee-values), dehydroamino (entries 7.7, 7.8; best ligand PEt_2-trap, unusual p and T effects), and itaconic acid derivatives (entry 7.9). *β*-Hydroxy–*α*-amino acids and *α,β*-diamino acids can be prepared via asymmetric hydrogenation of tetrasubstituted alkenes **14–16** with respectable de-values of 99–100% and ee-values of 97% and 82%, respectively, but low catalyst activities (entry 7.10). Also described was the hydrogenation of an indinavir intermediate **17** (entry 7.11).

25.6
Major Applications of Ferrocene Diphosphine-Based Catalysts

As can be seen in the preceding section, ferrocene-based complexes are very versatile ligands for the enantioselective hydrogenation of a variety of alkenes. One reason for this is undoubtedly the modularity of most of the described ligand families which allows them to influence the activity and enantioselectivity in an extraordinarily broad range. In the following section a short overview is provided of substrates where ferrocene-based ligands define the state of the art not only for alkene hydrogenation but also for the enantioselective reduction of C=O and C=N groups. A comparison with other classes of ligands can be found in an above-mentioned review [3].

25.6.1
Hydrogenation of Substituted Alkenes

Rh complexes of ferrocene-based ligands are very effective for the hydrogenation of several types of α- and β-dehydroamino (Fig. 25.17, structures **18**–**22**), enamides (**23**) and enol acetates (**24**), as well as for itaconic acid derivatives (**25**, **26**) and α,β-unsaturated acids (**27**). Of particular interest are substrates which have unusual substituents (**19**, **21**) at the C=C moiety or are more sterically hindered than the usual model compounds (**20**, **27**). Cu complexes of ferrocenyl diphosphines are very effective for the reduction of nitroalkenes **28** and α,β-unsaturated ketones **29** with high chemoselectivity. Effective metal/ligand combinations with very high ee-values and often respectable TONs and TOFs are listed in Table 25.8. Several industrial applications have already been reported using Rh-josiphos and Ru-josiphos (see Fig. 25.10), as well as for Rh-bophoz (see Fig. 25.13) and Rh-walphos (see Fig. 25.14).

25.6.2
Hydrogenation of C=O and C=N Functions

Ferrocene-based complexes have some potential for the enantioselective reduction of ketones, but compared to other ligand classes this is relatively limited [3]. Rh complexes of bppfa, bophoz and josiphos are among the most selective catalysts for the hydrogenation of α-functionalized ketones (Table 25.9; Fig. 25.18, **30**–**32**). Ru complexes of walphos and ferrotane are quite effective for

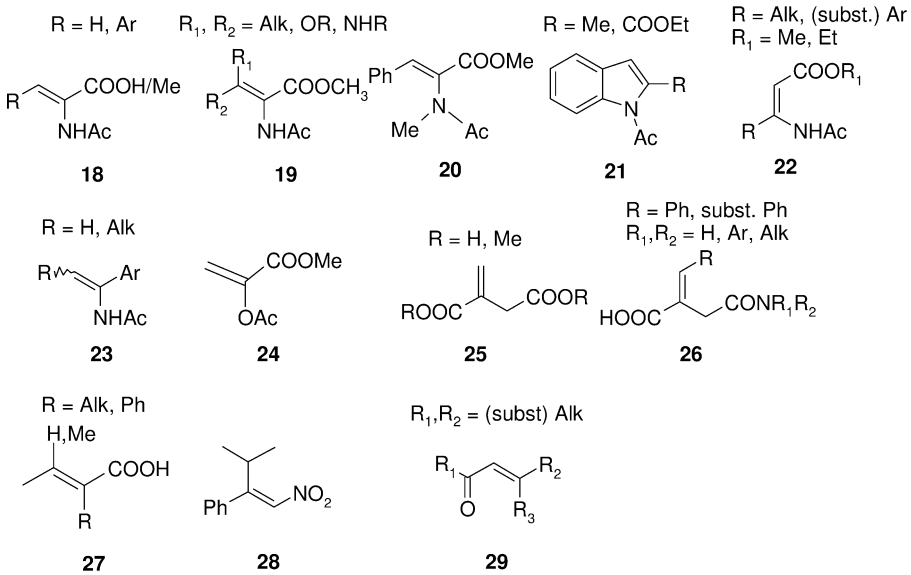


Fig. 25.17 Structures of substrates listed in Table 25.8.

Table 25.8 Best SCRs, TOF and ee-values for the reduction of selected functionalized alkenes (for substrates, see Fig. 25.17).

Sub-strate	Metal-ligand	TON	TOF [h^{-1}]	ee [%]
18	Rh-bophoz, Rh-josiphos, Rh-mandyphos, Rh-taniaphos, Rh-**L2**, Rh-**L4**	Up to 20 000	Up to 10 000	98–>99
19	Rh-trap	100 [a)]	4 [a)]	97
20	Rh-**L5**	200 [a)]	15 [a)]	96–98
21	Ru-taniaphos, Rh-trap	100–200 [a)]	25–200 [a)]	94–96
22	Rh-josiphos, Rh-taniaphos, Rh-**L11**	Up to 5000	Up to ~4000	92–>99
23	Rh-**L3**, Rh-taniaphos, Rh-**L11**	Up to 5000	Up to 6000	92–98
24	Rh-mandyphos, Rh-taniaphos, Rh-**L11**	Up to 10 000	Up to 20 000	95–98
25	Rh-josiphos, Rh-taniaphos, Rh-**L3**, Rh-**L4**	200 [a)]	>200 [a)]	97–99.9
26	Rh-ferrotane	Up to 20 000	Up to 7000	98–99
27	Rh-bppfa, Rh-mandyphos, Rh-walphos	Up to 5000	Up to ~800	95
28	Cu-josiphos	100 [a)]	~16 [b)]	94
29	Cu-josiphos, Cu-walphos	1640	10–80 [a)]	97–98

a) Standard test results, not optimized.

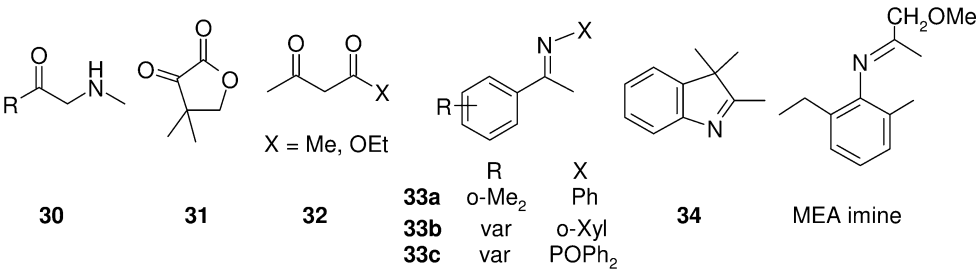


Fig. 25.18 Structures of ketone and imine substrates listed in Table 25.9.

β-keto esters and diketones **32**, though this is usually the domain of Ru-binap-type catalysts. Josiphos and f-binaphane however are the ligands of choice for the Ir-catalyzed hydrogenation of N-aryl imines such as **33** and **34**. Special mention should be made of the Ir-josiphos catalyst system which is able to hydrogenate MEA imine with TONs up to 2×10^6 [18].

Table 25.9 Best catalysts for the hydrogenation of C=O and C=N functions (for substrates, see Fig. 25.18).

Substrate	Metal-ligand (additive)	TON	TOF [h^{-1}]	ee [%]
30	Rh-bppfoh, bppfsh	200–2000	2–125	95–>99
31	Rh-bophoz, josiphos	100–200 [a)]	1 [a)]–>1000	97–99
32	Ru-walphos, ferrotane	5–200 [a)]	<1–25 [a]	95–99
33a	Ir-josiphos/I^-/H^+	200 [a)]	n.a.	96
33b	Ir-f-binaphane/I_2	100 [a)]	2 [a)]	>99
33c	Rh-josiphos	500	500	99
34	Ir-josiphos/I^-/H^+	250 [a)]	56 [a)]	93
MEA imine	Ir-josiphos/I^-/H^+	2 000 000	>400 000	80

a) Standard test results, not optimized.
n.a. = data not available.

Abbreviations

ACA	acetamido cinnamic acid
DMIT	dimethyl itaconate
ee	enantiomeric excess
ITA	itaconic acid
MAA	methyl acetamido acrylate
MAC	methyl esters of acetamido cinnamic acid
SCR	substrate:catalyst ratio
TOF	turnover frequency
TON	turnover number

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